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ORIGINAL INVESTIGATION

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The $GABA_A$ agonist gaboxadol improves the quality of post-nap sleep

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Abstract *Rationale:* Previous studies demonstrated that gaboxadol, a selective $GABA_A$ agonist, increases both non-REM sleep and EEG delta activity within non-REM sleep in rats and slow wave sleep (SWS) as well as low-frequency activity in the EEG within non-REM sleep in healthy humans under normal conditions. *Objective:* Because the hypnotic actions of drugs may be more readily demonstrated under conditions of poor sleep quality, we investigated the influence of gaboxadol on postnap sleep. *Methods:* In a randomized, placebo-controlled cross-over study using a late afternoon nap model, we assessed the effects of a single oral dose of 20 mg gaboxadol on disturbed nighttime sleep in young, healthy subjects. *Results:* Comparisons of visually scored sleep parameters between baseline and placebo postnap nights showed that the nap prolonged sleep latency, decreased total sleep time and SWS and attenuated delta, theta and alpha activity in the EEG within non-REM sleep. Compared with the placebo postnap night, gaboxadol tended to shorten sleep latency, significantly decreased intermittent wakefulness, increased total sleep time and SWS and enhanced delta and theta activity in the non-REM EEG. Furthermore, gaboxadol increased subjective sleep quality. *Conclusions:* These data show that gaboxadol counteracts the disrupting effects of a nap on subsequent sleep and suggest that, in addition to promoting deep sleep and sleep maintenance, gaboxadol is able to facilitate sleep initiation and thus, exhibits significant hypnotic actions under conditions in which sleep quality is experimentally reduced.

Keywords Gaboxadol · $GABA_A$ agonist · Sleep · EEG spectral analysis · Hypnotics

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Introduction

Various studies showed that the selective $GABA_A$ receptor agonist gaboxadol [4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol], also called THIP, influences sleep-wake behavior in rats. In this species, it increases time spend in non-rapid eye movement (non-REM) sleep, lengthens the duration of the non-REM sleep episodes and enhances slow wave activity (SWA) in the electroencephalogram (EEG) within non-REM sleep in a dose-related manner (Lancel and Faulhaber 1996; Lancel 1997; Lancel and Langebartels 2000). One study documented effects of gaboxadol on sleep in young, healthy subjects (Faulhaber et al. 1997). In this experiment, 20 mg gaboxadol, administered orally shortly before bedtime, markedly promoted slow wave sleep (stages 3 and 4; SWS), augmented low-frequency activity in the EEG within non-REM sleep and moderately increased sleep efficiency. It did not affect sleep onset latency or the amount of wakefulness. However, the quality of normal night sleep in young, good sleepers is usually already close to optimal. The sleep promoting action of drugs may more easily manifest itself under conditions of poor sleep quality. It is well established that daytime naps, presumably by decreasing the homeostatic pressure for sleep, reduce the quality of sleep during the subsequent night. Late afternoon as well as early evening naps have been demonstrated to decrease sleep efficiency, to prolong sleep onset latency, to reduce SWS and attenuate slow frequency components in the EEG within non-REM sleep (Karacan et al. 1970; Feinberg et al. 1985; Dijk et al. 1989; Werth et al. 1996). Thus, in good sleepers soporific effects of drugs may be more readily demonstrated in postnap night-time sleep. In the present experiment, we investigated the influence of 20 mg gaboxadol on the subjective and objective sleep quality in a model of disturbed sleep using a late afternoon nap.

Gaboxadol, which is currently developed by H. Lundbeck A/S for the treatment of insomnia, has an elimination half-life of 1.5–2 h and maximal plasma levels are reached 30 min after oral administration (Schultz et al. 1981).

Materials and methods

Subjects

Ten healthy young males (age range 21–32 years) participated in the study after being subjected to extensive psychiatric, physical and laboratory examinations. Criteria for exclusion from the experiment were subjective sleep disturbances, substance abuse, medical illness, abnormalities in blood chemistry, waking EEG or electrocardiogram, a personal or family history of psychiatric disorders, recent stressful life events, a transmeridian flight or shift-work during the preceding 3 months. Written informed consent was obtained from all subjects after procedures and possible side-effects of the drug were explained to them. The subjects were requested to maintain regular bedtimes and to abstain from alcohol prior to and during the study.

Study design

The experiment has been approved by the local ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The subjects slept in the darkened and sound-attenuated sleep laboratory during two study periods that were separated by at least 1 week. Each study period consisted of 3 consecutive nights: an adaptation, a baseline and a postnap night, each starting at 2300 hours and ending at 0700 hours. On the day between the baseline and postnap night, the subjects took a nap in the laboratory from 1600 until 1800 hours. On the postnap night the subjects were administered a gelatine capsule at 2230 hours containing either placebo (lactose) or 20 mg gaboxadol (H. Lundbeck A/S, Copenhagen, Denmark) according to a randomized, double-blind, cross-over design. Sleep was recorded during the baseline nights, scheduled naps and postnap nights. On the morning following the baseline and postnap nights, 15–30 min after arising, subjective sleep quality was assessed by a questionnaire and self-ratings on 10-cm visual bipolar analog scales.

Sleep recording

EEGs (C3-A2 and C4-A1; time constant 0.3 s, amplification 70 μV/cm, high- and low-pass filtering 0.53 and 70 Hz, –3 dB and –12 dB/octave), the submental electromyogram (EMG) and electrooculogram (EOG) were recorded on a Schwartzer ED 24 polygraph. Sleep stages were visually scored per 30-s epoch according to the criteria of Rechtschaffen and Kales (1968) by experienced raters who were unaware of the treatment. By means of a personal computer, the signals were sampled at 100 Hz by an 8-bit A/D converter and stored on disk. The C3-A2 EEG-derivation was submitted to a fast Fourier transformation. EEG power spectra were computed for consecutive rectangular windows of 256 samples (approximately 2.56 s), resulting in a frequency resolution of about 0.39 Hz between 0 and 50 Hz. EEG spectra were averaged over epochs of 12 consecutive windows (approximately 30.72 s). For the following epoch, the procedure stepped back 72 samples (0.72 s) to permit synchronization with the 30-s epochs of the visual scores. Epochs containing visually identified EEG artefacts as well as epochs scored as movement time were eliminated. Average EEG power densities and SWA (0.78–4.29 Hz) within non-REM sleep (stages 2, 3 and 4) were computed for each 2-h interval. Because of large inter-individual differences in absolute power, the data were normalized by expressing them as percentage of the average power in the same frequency band within non-REM sleep during the baseline nights.

Statistical evaluation

The baseline data did not differ significantly between the study periods. To reduce data, baseline estimates were pooled for each subject. Because of the ordinal data structure of the subjective sleep parameters, differences between the baseline and postnap placebo night and between the postnap placebo and gaboxadol night were analyzed with the non-parametric Wilcoxon matched pairs signed rank test. To approach normality in the visually scored sleep parameters, the data were transformed with a log transformation [y=log10(x+1)]. We then applied a one-factorial repeated measures analysis of variance (ANOVA, Greenhouse-Geisser correction) with treatment (three levels: baseline, postnap placebo and gaboxadol) as a within-subjects factor. When a significant “treatment” effect was found, tests with contrasts were employed to find out whether the baseline and/or the postnap gaboxadol data differed significantly from the postnap placebo night. To examine differences in EEG power densities within non-REM sleep a two-factorial repeated measures ANOVA, with treatment (three levels) and time (four levels: four 2-h intervals) as within-subjects factors, was applied. When appropriate, one-factorial ANOVAs and tests with contrasts were employed.

Results

Subjective sleep quality

No significant difference was found between the baseline and postnap placebo night in the subjective assessments of sleep latency, total sleep time, number of awakenings, sleep quality and intensity and fitness upon awakening (Table 1). Compared with placebo, gaboxadol significantly reduced sleep latency as well as the number of awakenings and increased both total sleep time and sleep quality.

Visually scored sleep parameters

The naps did not differ in any respect between the study periods. Average total sleep time was 75.9±35.2 min, which consisted of 9.5±4.8 min stage 1, 35.6±17.0 min stage 2, 20.4±16.0 min SWS and 10.2±9.8 min REM sleep.

Analysis of the visually scored sleep parameters during the baseline, postnap placebo and gaboxadol nights

Table 1 Subjective sleep quality. Values are means±SD (*n*=10). Baseline, mean of 2 baseline nights

	Baseline	Postnap	
		Placebo	Gaboxadol
Open questions			
Estimated sleep latency (min)	37.6±33.2	52.0±35.8	37.5±40.2*
Estimated total sleep time (h)	6.7±0.8	6.4±0.9	7.0±0.8*
Perceived number of awakenings	3.0±1.6	3.5±1.6	2.0±1.6*
10-cm visual bipolar analog scales			
Self-rated sleep quality	6.0±2.2	5.6±1.7	7.4±1.9*
Perceived sleep intensity	6.9±2.1	6.4±2.3	7.6±1.8
Rated fitness upon awakening	6.6±2.1	6.8±1.9	6.9±2.2

* Significant difference from placebo (*P*<0.05, Wilcoxon matched pairs signed rank test). Self-rated sleep quality: bad (0) versus good (10). Perceived sleep intensity: superficial (0) versus deep (10). Rated fitness upon awakening: numb (0) versus fresh (10)

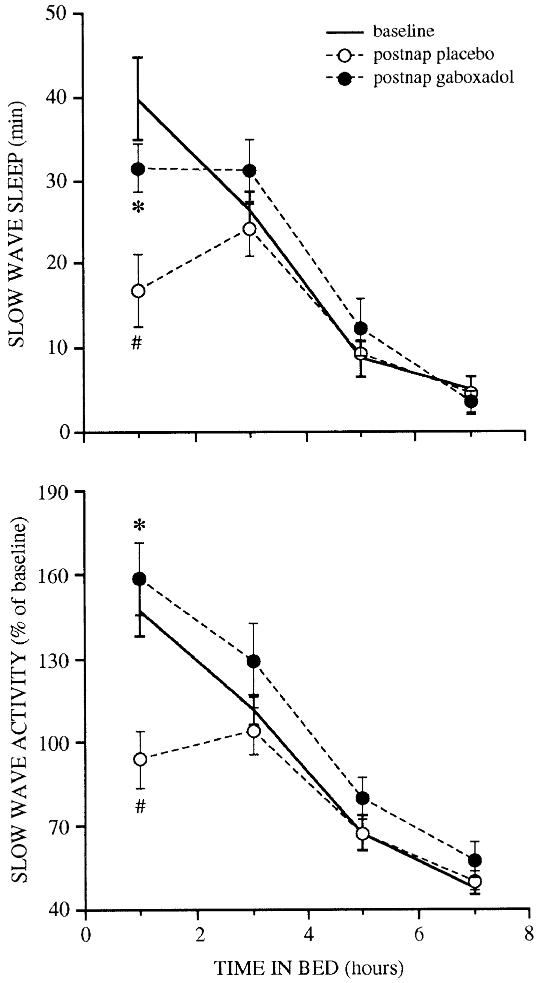

Fig. 1 Time course of slow wave sleep and average slow wave activity (SWA) in the EEG within non-REMS during the baseline and postnap placebo and gaboxadol night. Values are means±SEM (*n*=10) and are plotted in the middle of the 2-h intervals. Baseline, mean of 2 baseline nights. For each subject, SWA data were expressed as percentage of average SWA within non-REMS during the entire baseline nights. # Significant difference from baseline and * from postnap placebo (*P*<0.05, tests with contrasts)

yielded a significant treatment effect for total sleep time [*F*(2,18)=6.3, *P*=0.02], sleep efficiency [*F*=5.9, *P*=0.02], sleep onset latency [*F*=10.9, *P*=0.003], the number of awakenings [*F*=7.6, *P*=0.006], total wakefulness as well as wakefulness after sleep onset [*F*=5.8, *P*=0.02 and *F*=8.8, *P*=0.003 respectively], SWS [*F*=16.1, *P*=0.002] and stage 4 [*F*=8.6, *P*=0.003]. Comparisons of the baseline and postnap placebo night showed that the afternoon nap significantly prolonged sleep onset latency, on average by 25 min, reduced total sleep time and increased wakefulness, both approximately by 27 min (Table 2). Consequently, sleep efficiency was decreased, on average by 5.6%. While stage 1 and 2 were not influenced, the nap produced a decrease in SWS, particularly in stage 4, that mainly occurred during the first 2-h interval of the sleep period (Fig. 1). The latency to REM sleep and the total amount of REM sleep were unchanged.

Table 2 Visually scored sleep variables. Values are means±SD (*n*=10). Baseline, mean of 2 baseline nights. *WASO* wakefulness after sleep onset

	Baseline	Postnap	
		Placebo	Gaboxadol
Total sleep time (min)	440.3±31.3	413.2±45.3#	441.1±22.8*
Sleep efficiency (%)	91.8±6.7	86.2±9.7#	92.2±4.3*
Sleep onset latency (min)	17.7±10.8	42.6±25.2#	28.5±12.4
REM sleep latency (min)	84.7±23.1	65.1±32.6	72.1±31.6
Number of awakenings	11.7±4.4	12.5±5.6	8.0±5.2*
Wakefulness (min)	37.7±31.6	64.0±46.5#	36.0±19.3*
WASO (min)	23.4±22.1	24.5±28.8	11.6±12.4*
Stage 1 (min)	38.7±17.7	37.9±23.9	32.9±21.2
Stage 2 (min)	222.5±20.2	216.5±31.5	220.8±27.2
Slow wave sleep (min)	79.6±25.7	54.2±21.5#	78.4±24.4*
Stage 3 (min)	41.3±9.3	34.2±13.8	37.1±13.5
Stage 4 (min)	38.3±26.1	20.0±14.3#	41.3±15.8*
REM sleep (min)	94.1±23.8	98.7±35.7	103.1±26.0
Movement time (min)	5.5±2.4	6.0±3.8	6.1±3.1

# Significant difference from baseline and * from postnap placebo (*P*<0.05, tests with contrasts)

Gaboxadol markedly affected postnap sleep. Compared with placebo, gaboxadol significantly increased total sleep time and sleep efficiency (Table 2). Further, it tended (*P*=0.08) to shorten sleep onset latency, significantly reduced the number of nocturnal awakenings, total wakefulness as well as waking after sleep onset. Moreover, it promoted SWS and within SWS, especially stage 4 during the first 2-h interval (Fig. 1). Gaboxadol neither affected REM sleep latency nor the total amount of REM sleep.

EEG spectral power densities

Analysis of SWA within non-REM sleep yielded a significant effect of treatment [*F*(2,18)=11.0, *P*=0.002], time [*F*(3,27)=80.2, *P*<0.0001] and of treatment by time [*F*(36,54)=3.6, *P*=0.02]. Post hoc testing showed that treatment significantly affected SWA during the first 2-h interval [*F*(2,18)=10.5, *P*=0.001]. During this time period, SWA was significantly lower in the postnap placebo than in the baseline night, while it was higher in the gaboxadol than in the placebo night (Fig. 1).

ANOVAs of EEG power densities in each of the 0.39 Hz bins revealed a significant (*P*<0.05) effect of treatment for all frequency bands between 0.78 and 10.5 Hz, of time for nearly all frequencies and of treatment by time for the frequency bands from 0.78 up to 5.9 Hz. During the first 2-h interval, EEG power densities in the frequencies below 11 Hz were significantly influenced by treatment, which was due to low values in the postnap placebo night compared to the baseline as well as to the postnap gaboxadol night (Fig. 2). During the following 2-h intervals, low-frequency activity did not differ significantly between the treatments, while theta activity remained slightly higher in the gaboxadol than in the placebo night.

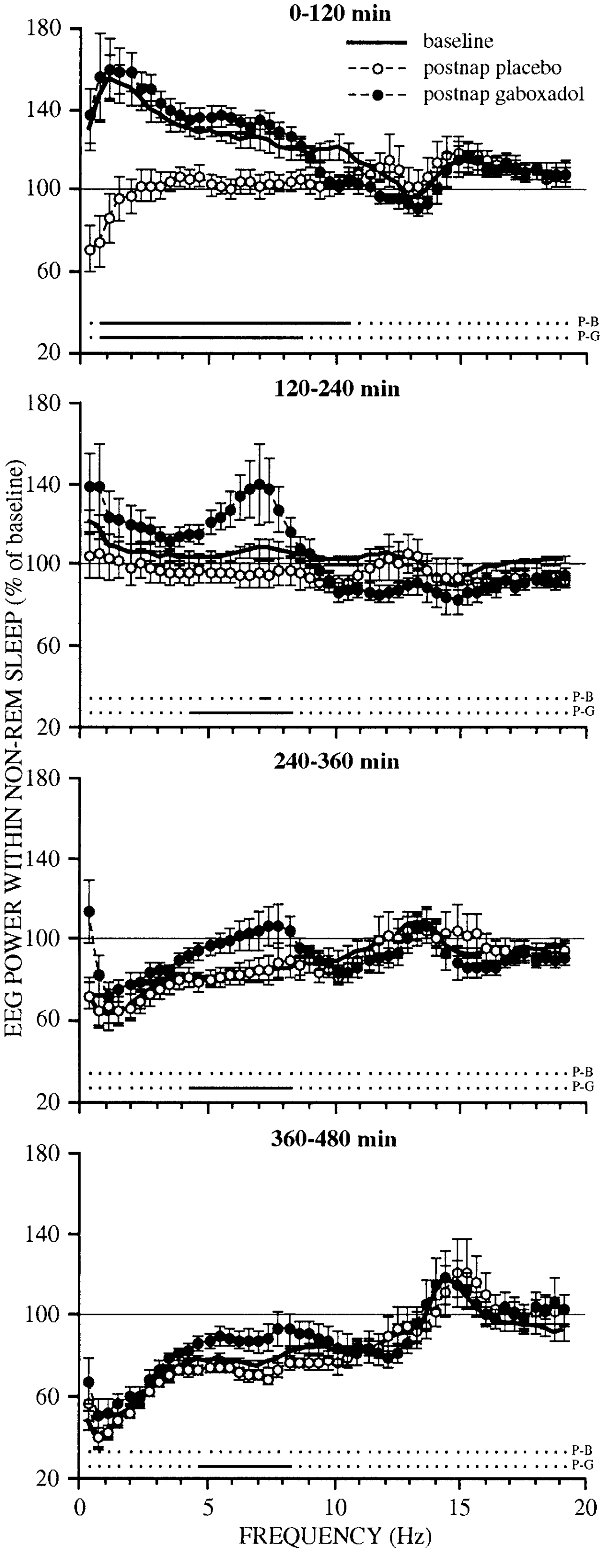

Fig. 2 EEG power densities within non-REMS per 2-h interval during the baseline and postnap placebo and gaboxadol night. Values are means±SEM (n=10). Baseline, mean of 2 baseline nights. For each subject, the values were expressed as percentage of average EEG power density in the same frequency band within non-REMS during the entire baseline nights. *Dots* at the bottom of the graphs denote frequency bands. *Lines* through the dots refer to frequency bands in which power differed significantly between postnap placebo and baseline (P-B) or postnap gaboxadol (P-G) (P<0.05, tests with contrasts)

Discussion

Our subjects generally displayed a good sleep quality during the baseline nights. Typically for young healthy people, they fell asleep within the normal time range, exhibited little intermittent wakefulness and a considerable amount of SWS, particularly during the first half of the night.

All subjects were able to enter sleep between 1600 and 1800 hours. While the late afternoon nap barely influenced subjective quality, it clearly deteriorated objective quality of subsequent night sleep. The nap more than doubled objective sleep onset latency and, consequently, reduced both total sleep time and sleep efficiency. It did not alter wakefulness after sleep onset. Furthermore, the nap decreased the intensity of subsequent non-REM sleep, as indexed by reductions in SWS and in delta, theta, alpha activity in the EEG. All these changes mainly occurred during the first 2 h of the sleep period. Despite differences in the time of day and duration of scheduled naps, the present data are in good accordance with previous studies (Karacan et al. 1970; Feinberg et al. 1985; Dijk et al. 1989; Werth et al. 1996) and indicate that naps taken towards the end the day reliably disturb sleep during the following night. Because extended wakefulness exerts opposite effects on sleep – sleep deprivation is well established to shorten sleep onset latency, increase total sleep time and SWS and to augment low-frequency activity in the EEG within non-REM sleep (Borbély et al. 1981; Dijk et al. 1990) – the impact of daytime naps are presumably due to a reduction in the homeostatic drive for sleep.

We anticipated that in good sleepers the hypnotic action of drugs may be more readily demonstrated in disturbed sleep. Therefore, we investigated the influence of gaboxadol on nocturnal sleep following a late afternoon nap and compared it with placebo postnap sleep. Although one subject reported to have had a mild headache during 5 min after gaboxadol ingestion, the employed dose of 20 mg was generally well tolerated. Gaboxadol influenced various subjectively and objectively assessed sleep parameters. With respect to the former, gaboxadol significantly shortened self-estimated sleep latency, by about 15 min, reduced the number of perceived awakenings and increased total sleep time, on average by more than 30 min, which were associated with an increase in self-rated sleep quality. In keeping with the subjective changes, gaboxadol significantly increased visually scored total sleep time, approximately by 30 min, which was both due to a tendency towards areduction of sleep onset latency and a decrease in intermittent wakefulness. Consequently, it increased the sleep efficiency index, on average by 6%. These findings indicate that gaboxadol has hypnotic properties, in that it is able to increase sleep initiation as well as sleep maintenance. Furthermore, gaboxadol significantly increased SWS, by approximately 25 min, and powerfully augmented low-frequency activity in the EEG within non-REM sleep. These observations strongly suggest that gaboxadol promotes deep sleep. Finally, gaboxadol did not affect the latency to or the distribution of REM sleep.

The previous study, in which the influence of the same dose of gaboxadol on normal night sleep in a comparable group of subjects was investigated, yielded less prominent effects on sleep architecture. In contrast to the present data, it did not influence sleep onset latency nor intermittent wakefulness and, consequently, evoked only a minor increase in sleep efficiency of about 3% (Faulhaber et al. 1997). Yet, its effects on the EEG signals within non-REM sleep were rather similar, in that gaboxadol produced a marked increase in SWS and augmented delta, and more persistently so, theta activity. The only notable difference is that it persistently depressed EEG power density in the sigma bands, the frequency range of sleep spindles. It is unclear why such an effect is absent in the present data. The present results show that gaboxadol, in addition to its promotion of deep sleep, is able to increase the initiation and consolidation of nocturnal sleep in young healthy subjects, whose sleep pressure was experimentally reduced by a preceding late afternoon nap. Since these effects could not be observed during baseline conditions, these findings support the postulate that in good sleepers, soporific properties of drugs are more readily demonstrated in disturbed sleep.

Concerning the profile of its effects, gaboxadol effectively counteracted the disrupting effects of the nap on subsequent sleep. Due to a reduction in sleep debt, the late afternoon nap prolonged sleep onset latency, thereby increasing wakefulness and reducing total sleep time, and decreased SWS as well as low-frequency activity in the EEG within non-REMS. Gaboxadol had exactly the opposite effects and returned all variables to baseline levels. Additionally, gaboxadol slightly reduced the number of awakenings and intermittent wakefulness, which may underlie the observed increase in self-rated sleep quality, and produced a longer-lasting enhancement of theta activity. The observation that gaboxadol reverses the sleep changes induced by the nap extends the information suggesting that it mimics the effects of a physiological increase in sleep need.

The influence of gaboxadol on sleep seems to differ from that of benzodiazepine hypnotics. The latter reliably increase the ability to fall and to stay asleep, to decrease SWS, attenuate slow frequency components in the EEG within non-REM sleep and to transiently suppress REM sleep in young healthy subjects during a normal night (reviewed in Lancel 1999). An earlier study, delineating the effect of a number of drugs on postnap sleep, showed that the benzodiazepine temazepam significantly shortened sleep onset latency and increased total sleep time, but, in contrast to gaboxadol, did not affect SWS and prominently decreased power in the delta and theta bands in non-REM sleep (Dijk et al. 1989). Intriguingly, the effects of gaboxadol on EEG power spectra in non-REM sleep to some extent resemble the modifications induced by selective 5-HT$_2$ antagonists. During baseline conditions, both ritanserin, seganserin and SR 46349B evoke robust increases in SWS, though at the expense of stage 2 and, to a lesser extent, of REM sleep (Idzikowski 1989; Landolt et al. 1999). SR 46349B has also been shown to enhance delta and low-theta activity and to attenuate spindle frequency activity in the EEG within non-REM sleep. Finally, seganserin appeared to reduce intermittent wakefulness and increase SWS and spectral power density in some theta frequency bands during postnap sleep (Dijk et al. 1989). Although their working mechanisms are still obscure, the observation that both the 5-HT$_2$ antagonists and the GABA$_A$ agonist gaboxadol promote SWS and enhance slow frequency components in the non-REM sleep-specific EEG suggests that these compounds may share effects on neuronal processes underlying the generation/synchronization of slow waves.

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